

# daily tadalafil

## Line Extension

### Beware medicalisation of human existence

#### ● “On demand” use is safer.



NOTHING NEW

Tadalafil (Cialis<sup>®</sup>, Lilly), a phosphodiesterase type 5 inhibitor, was first marketed in France in 2003, in 10 mg and 20 mg oral tablets for “on demand” treatment of erectile disorders. We concluded that it did not provide a significant advantage over sildenafil (1).

In late 2007, Lilly added two lower dose strengths (2.5 mg and 5 mg of tadalafil) to its range of Cialis<sup>®</sup> products and promoted them for once-daily use. The posology section of the SPC mentions that in “responder patients to on-demand regimen who anticipate a frequent use of Cialis (i.e., at least twice weekly) a once daily regimen with the lowest doses of Cialis might be considered suitable” (a)(2,3). The SPCs for the 10 mg and 20 mg tadalafil tablets state that they are “not recommended for continuous daily use” (3).

**No direct comparison with “on demand” use.** According to the scientific discussion of the European Committee for Medicinal Products for Human use (CHMP), this new method of administration is based on the results of 3 randomised double-blind placebo-controlled trials evaluating daily tadalafil doses of 2.5 mg, 5 mg and 10 mg (4).

Two trials lasting 3 and 6 months included a total of 555 patients with an average age of 56 to 60 years who had erectile disorders of organic and/or psychological origin and a history of hypertension, cardiovascular disease or diabetes. The proportions of patients who achieved an erection adequate for satisfactory intercourse were 30% and 36% in the placebo arms, versus 50% with 2.5 mg of tadalafil, 57% and 67% with 5 mg of tadalafil, and 72% with 10 mg of tadalafil (statistically significant difference between tadalafil and placebo) (4).

In another 3-month trial that included 298 diabetic patients with an average age of 57 years, the proportion of patients who had an erection adequate for satisfactory intercourse was 28% with placebo, 46% with 2.5 mg of tadalafil and 41% with 5 mg of tadalafil

(statistically significant difference) (4).

Unfortunately, daily use has not been compared with “on demand” use (3,4). An indirect comparison of placebo-controlled trials (b) suggests that the proportion of patients who achieved an erection adequate for satisfactory intercourse is lower with daily use of tadalafil 2.5 mg (50%) or 5 mg (57% and 67%) than with “on demand” use of 10 mg (61%) or 20 mg (75%) (1,4).

**Adverse effects.** According to the CHMP, the frequency of adverse effects in clinical trials of daily use of tadalafil was similar to that reported in clinical trials of “on demand” tadalafil (between 46% and 50%) (3). These adverse effects include headache, dyspepsia, back pain, myalgia, and nasal congestion (1,3,4). Neurosensory effects (altered hearing and vision) have also been reported with phosphodiesterase type 5 inhibitors (4,5).

The CHMP has asked the company to implement a risk management plan for elderly patients using tadalafil on a daily basis (4). On 8 February 2008, no description of the plan was available on either the French or European drug regulatory websites.

Tadalafil is metabolised by the cytochrome P450 isoenzyme CYP 3A4, hence a high risk of interactions (6). Tadalafil in combination with nitrate derivatives is contraindicated, and concurrent administration with alphablockers should be avoided because of the risk of arterial hypotension (3).

**Unnecessary continuous medication.** There is no evidence that daily use of tadalafil offers any advantages in terms of efficacy or adverse effects. The lack of long-term safety data on daily use of tadalafil calls for caution. It is better to continue using tadalafil “on demand”, at the minimum dose required by each individual patient.

This promotion of daily tadalafil is another example of the tendency to promote continuous medication in order to maintain “normality” when the boundary between the normal and the pathological is far from clear (7).

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#### tadalafil (Cialis<sup>®</sup>)

Tablets

- 2.5 mg and 5 mg of tadalafil per tablet

*a- In France, the packaging for 2.5 mg and 5 mg Cialis<sup>®</sup> tablets tends to encourage continuous medication: “For oral administration once a day” is printed on the main face of the box; and “How to take Cialis once a day” is prominently displayed (in colour/against a coloured background) and a dosing schedule appears once the transparent tamper-proof film is removed (our translation).*

*b- A combined analysis of 5 placebo-controlled trials of “on demand” tadalafil treatment, lasting 3 months and including a total of 1112 patients with a history of hypertension, diabetes mellitus, coronary heart disease or depression, showed that the proportion of patients with an erection sufficient for full intercourse was 32% with placebo, 36% with 2.5 mg of tadalafil, 42% with 5 mg of tadalafil, 61% with 10 mg of tadalafil, and 75% with 20 mg of tadalafil (all doses were significantly more effective than placebo) (1).*

#### Selected references from Prescrire’s literature watch.

- 1- Prescrire Editorial Staff “Tadalafil” *Prescrire Int* 2003; 12 (68): 213-215.
- 2- Lilly “Dysfonction érectile - Nouveau mode de prise” October 2007: 4 pages.
- 3- European Commission “RCP-Cialis 2,5 mg et 5 mg comprimés” 18 October 2007: 24 pages in total.
- 4- EMEA-CHMP “EPAR Cialis (revision 5) - Scientific discussion 436/X/26-27”: 21 pages; posted on the EMEA website on 31 October 2007.
- 5- Prescrire Rédaction “Sildénafil, tadalafil, vardénafil: surdité subite” *Rev Prescrire* 2008; 28 (291): 23.
- 6- Prescrire Editorial Staff “Fiche 1A. Inhibiteurs et substrats de l’isoenzyme CYP 3A4 du cytochrome P450” *Rev Prescrire* 2007; 27 (290 suppl. interactions médicamenteuses).
- 7- Prescrire Editorial Staff “Shaping disease : marketing departments flex their wings” *Prescrire Int* 2007; 16 (90): 174.